



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification:</b> <b>C07D 487/08, A61K 31/395,</b> <b>A61K 31/439, A61K 31/551,</b> <b>A61K 49/00, A61P 25/28,</b> <b>A61P 25/30, A61P 29/00,</b> <b>C07D 471/08</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/66586</b> <b>(43) International Publication Date:</b> 09 November 2000 (09.11.2000)
<b>(21) International Application Number:</b> PCT/DK00/00211 <b>(22) International Filing Date:</b> 27 April 2000 (27.04.2000) <b>(30) Priority Data:</b> PA 1999 00602 04 May 1999 (04.05.1999) DK <b>(60) Parent Application or Grant</b> NEUROSEARCH A/S [/]; (). PETERS, Dan [/]; (). NIELSEN, Simon, Feldbæk [/]; (). OLSEN, Gunnar, M. [/]; (). NIELSEN, Elsebet, Ostergaard [/]; (). PETERS, Dan [/]; (). NIELSEN, Simon, Feldbæk [/]; (). OLSEN, Gunnar, M. [/]; (). NIELSEN, Elsebet, Ostergaard [/]; (). NEUROSEARCH A/S; ().	<b>Published</b>	
<b>(54) Title: HETEROARYL DIAZABICYCLOALKANES, THEIR PREPARATION AND USE</b> <b>(54) Titre: DIAZABICYCLOALCANES HETEROARYLES, LEUR PREPARATION ET LEUR UTILISATION</b>  <b>(57) Abstract</b> <p>The present invention relates to novel heteroaryl diazabicycloalkane derivatives represented by general formula (I), any of its enantiomers or any mixture thereof, an N oxide thereof, a pharmaceutically acceptable salt thereof, in a labelled or un-labelled form, which are found to be cholinergic ligands at the nicotinic Acetyl Choline Receptors. Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neurodegeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.</p> <b>(57) Abrégé</b> <p>La présente invention concerne de nouveaux dérivés de diazabicycloalcane hétéroaryle représentés par la formule générale (I), (formule I) n'importe quels énantiomères ou mélanges de celui-ci, son N-oxyde, son sel pharmaceutiquement acceptable, sous forme étiquetée ou non étiquetée, qui se sont avérés être des ligands cholinergiques sur les récepteurs nicotiniques de l'acétylcholine. Grâce à leur profil pharmacologique, les composés de l'invention pourraient servir au traitement de maladies et de troubles aussi variés que ceux liés au système cholinergique du système nerveux central (SNC), ceux liés à la contraction des muscles lisses, des maladies et de troubles endocriniens, des maladies et de troubles liés à la neurodégénération, des maladies et de troubles liés à l'inflammation, à la douleur et au symptôme de sevrage provoqué par la cessation d'abus d'intoxicants.</p>		

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<p>(21) International Application Number: PCT/DK00/00211 (22) International Filing Date: 27 April 2000 (27.04.00)  (30) Priority Data: PA 1999 00602 4 May 1999 (04.05.99) DK  (71) Applicant (for all designated States except US): NEUROSEARCH A/S [DK/DK]; 93 Pederstrupvej, DK-2750 Ballerup (DK).  (72) Inventors; and (75) Inventors/Applicants (for US only): PETERS, Dan [SE/DK]; NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). NIELSEN, Simon, Feldbæk [DK/DK]; NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). OLSEN, Gunnar, M. [DK/DK]; NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). NIELSEN, Elsebet, Østergaard [DK/DK]; NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK).  (74) Common Representative: NEUROSEARCH A/S; Patent Department, 93 Pederstrupvej, DK-2750 Ballerup (DK).</p>	<p>(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	

(54) Title: HETEROARYL DIAZABICYCLOALKANES, THEIR PREPARATION AND USE

(57) Abstract

The present invention relates to novel heteroaryl diazabicycloalkane derivatives represented by general formula (I), any of its enantiomers or any mixture thereof, an N oxide thereof, a pharmaceutically acceptable salt thereof, in a labelled or un-labelled form, which are found to be cholinergic ligands at the nicotinic Acetyl Choline Receptors. Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neurodegeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

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**Description**

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**HETEROARYL DIAZABICYCLOALKANES, THEIR PREPARATION AND USE****TECHNICAL FIELD**

The present invention relates to novel heteroaryl diazabicycloalkane derivatives which are found to be cholinergic ligands at the nicotinic acetyl choline receptors.

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neurodegeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

**BACKGROUND ART**

The endogenous cholinergic neurotransmitter, acetylcholine, exert its biological effect via two types of cholinergic receptors, the muscarinic Acetyl Choline Receptors (mAChR) and the nicotinic Acetyl Choline Receptors (nAChR).

As it is well established that muscarinic acetyl choline receptors dominate quantitatively over nicotinic acetyl choline receptors in the brain area important to memory and cognition, and much research aimed at the development of agents for the treatment of memory related disorders have focused on the synthesis of muscarinic acetyl choline receptor modulators.

Recently, however, an interest in the development of nAChR modulators has emerged. Several diseases are associated with degeneration of the cholinergic system i.e. senile dementia of the Alzheimer type, vascular dementia and cognitive impairment due to the organic brain damage disease related directly to alcoholism. Indeed several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency or a serotonergic deficiency.

**SUMMARY OF THE INVENTION**

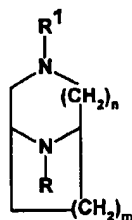
The present invention is devoted to the provision novel nicotinic receptor modulators, which modulators are useful for the treatment of diseases or disorders related to the cholinergic receptors, and in particular the nicotinic acetyl choline receptor (nAChR).

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the

cholinergic system of the central nervous system (CNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neurodegeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

The compounds of the invention may also be useful as diagnostic tools or monitoring agents in various diagnostic methods, and in particular for *in vivo* receptor imaging (neuroimaging), and they may be used in labelled or unlabelled form.

In its first aspect the invention provides novel diazabicycloalkane derivatives represented by the general Formula I



any of its enantiomers or any mixture thereof, an N oxide thereof, a pharmaceutically acceptable salt thereof, in a labelled or un-labelled form,

wherein,

n is 2 or 3; and

m is 1, 2 or 3; and

one of R and R¹ represents hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, or aralkyl; and

the other of R and R¹ represents a monocyclic 5 to 6 membered heterocyclic group,

which monocyclic heterocyclic group may be substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl, alkoxy, hydroxyalkoxy, alkoxyalkoxy, cycloalkoxy, cycloalkoxyalkoxy, alkenyl, alkenoxy, alkoxyalkenyl, alkynyl, alkynoxy, alkoxyalkynyl, alkylthio, alkenylthio, alkynylthio, alkylseleno, alkenylseleno, alkynylseleno, methylenedioxy, trifluoromethanesulfonyloxy, halogen, -OH, -CF₃, -OCF₃, -CN, amino, nitro, oxime, alkyloxime, acyloxime, or a group of the formula -COOR³, -CONR²R³, -NH-CO₂R², -NHCO-R², -OCO-NR²R³; in which formulae R² and R³ independently of each another represents hydrogen or alkyl; or

which monocyclic heterocyclic group may be substituted with an aryl group, which aryl group is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF₃, -OCF₃, -CN, amino, nitro, oxime, alkyloxime, or acyloxime; or

which monocyclic heterocyclic group may be substituted with a group of the formula "-X-alkyl-Y-alkyl", wherein X and Y independently of each another represents O (epoxy), S, NH, N-alkyl or Se, and the alkyl group is optionally substituted with alkoxy, or thioalkoxy; or

which monocyclic heterocyclic group may be substituted with a group of the formula "-X-(ALK)<sub>o</sub>-aryl", wherein X represents O, S, NH, N-alkyl or Se; "ALK" represents alkyl, alkenyl or alkynyl; o is 0 or 1; and aryl is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro oxime, alkyloxime, acyloxime; or

which monocyclic heterocyclic group may be substituted with a group of the formula "-X-(ALK)<sub>o</sub>-Z", wherein X represents O, S, NH, N-alkyl or Se; "ALK" represents alkyl, alkenyl or alkynyl; o is 0 or 1; and Z represents a 5- or 6-membered monocyclic heterocyclic group, which group is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or acyloxime; or

which monocyclic heterocyclic group may be substituted with another monocyclic 5 to 6 membered heterocyclic group, which additional heterocyclic group is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or acyloxime; or

which monocyclic heterocyclic group may be substituted with a group of the formula "(ALK)<sub>o</sub>-HET", wherein "ALK" represents alkyl, alkenyl or alkynyl; o is 0 or 1; and "HET" represents a non-aromatic heterocyclic group; or

the other of R and R<sup>1</sup> represents a **bicyclic heterocyclic group**, composed of a 5 to 6 membered monocyclic heterocyclic group fused to a benzene ring, and

which bicyclic heterocyclic group may be substituted one or more times with

alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; alkoxy-alkoxy; cycloalkoxy; alkenoxy; alkynoxy; methylenedioxy; halogen; -OH; -CF<sub>3</sub>; -OCF<sub>3</sub>; -CN; amino; nitro; oxime; alkyloxime; or acyloxime;

an aryl group, which aryl group is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or acyloxime;

a monocyclic 5- to 6-membered heterocyclic group, which heterocyclic group is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl

alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or acyloxime; or

R and/or R<sup>1</sup>, together with the nitrogen atom to which they are attached, represent an alkyl-onium salt, a dialkyl-onium salt, a cycloalkyl-onium salt, an alkyl-cycloalkyl-onium salt, a dicycloalkyl-onium salt, an alkyl-cycloalkylalkyl-onium salt, a cycloalkyl-cycloalkylalkyl-onium salt, or a dicycloalkylalkyl-onium salt.

In another aspect the invention provides pharmaceutical compositions comprising a therapeutically-effective amount of a diazabicycloalkane derivative of the invention, or pharmaceutically-acceptable addition salts thereof, together with at least one pharmaceutically-acceptable carrier or diluent.

In a third aspect the invention relates to the use of the diazabicycloalkane derivatives of the invention for the manufacture of a pharmaceutical composition for the diagnosis, treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the activity of nAChR modulators.

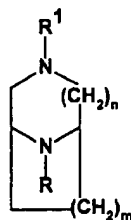
In a fourth aspect the invention provides a method for diagnosis, treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to the activity of nAChR modulators, comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a diazabicycloalkane derivative of the invention.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

## DETAILED DISCLOSURE OF THE INVENTION

### Diazabicycloalkane Derivatives

In a first aspect novel diazabicycloalkane derivatives are provided. The diazabicycloalkane derivatives of the invention may be represented by the general Formula I



any of its enantiomers or any mixture thereof, an N oxide thereof, a pharmaceutically acceptable salt thereof, in a labelled or un-labelled form,



wherein,

n is 2 or 3; and

m is 1, 2 or 3; and

one of R and R<sup>1</sup> represents hydrogen, alkyl, cycloalkyl, cycloalkylalkyl,

5 alkenyl, alkynyl, aryl, or aralkyl; and

the other of R and R<sup>1</sup> represents a **monocyclic 5 to 6 membered heterocyclic group,**

which monocyclic heterocyclic group may be substituted one or more times  
15 with alkyl, cycloalkyl, cycloalkylalkyl, alkoxy, hydroxyalkoxy, alkoxyalkyl,  
10 cycloalkoxy, cycloalkoxyalkoxy, alkenyl, alkenoxy, alkoxyalkenyl, alkynyl, alkynoxy,  
alkoxyalkynyl, alkylthio, alkenylthio, alkynylthio, alkylseleno, alkenylseleno,  
alkynylseleno, methylenedioxy, trifluoromethanesulfonyloxy, halogen, -OH, -CF<sub>3</sub>,  
20 -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, acyloxime, or a group of the formula  
-COOR<sup>3</sup>, -CONR<sup>2</sup>R<sup>3</sup>, -NH-CO<sub>2</sub>R<sup>2</sup>, -NHCO-R<sup>2</sup>, -OCO-NR<sup>2</sup>R<sup>3</sup>; in which formulae R<sup>2</sup> and  
15 R<sup>3</sup> independently of each another represents hydrogen or alkyl; or

which monocyclic heterocyclic group may be substituted with an aryl group,

which aryl group is optionally substituted one or more times with alkyl, cycloalkyl,  
25 cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy,  
methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or  
20 acyloxime; or

which monocyclic heterocyclic group may be substituted with a group of the  
30 formula "-X-alkyl-Y-alkyl", wherein X and Y independently of each another represents  
O (epoxy), S, NH, N-alkyl or Se, and the alkyl group is optionally substituted with  
alkoxy, or thioalkoxy; or

25 which monocyclic heterocyclic group may be substituted with a group of the  
35 formula "-X-(ALK)<sub>o</sub>-aryl", wherein X represents O, S, NH, N-alkyl or Se; "ALK"  
represents alkyl, alkenyl or alkynyl; o is 0 or 1; and aryl is optionally substituted one or  
more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy,  
40 alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro  
30 oxime, alkyloxime, acyloxime; or

which monocyclic heterocyclic group may be substituted with a group of the  
45 formula "-X-(ALK)<sub>o</sub>-Z", wherein X represents O, S, NH, N-alkyl or Se; "ALK" represents  
alkyl, alkenyl or alkynyl; o is 0 or 1; and Z represents a 5- or 6-membered monocyclic  
heterocyclic group, which group is optionally substituted one or more times with alkyl,  
35 cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy,  
methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or  
acyloxime; or

50 which monocyclic heterocyclic group may be substituted with another  
monocyclic 5 to 6 membered heterocyclic group, which additional heterocyclic group

is optionally substituted on or more times with alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or acyloxime; or

which monocyclic heterocyclic group may be substituted with a group of the formula "(ALK)<sub>o</sub>-HET", wherein "ALK" represents alkyl, alkenyl or alkynyl; o is 0 or 1; and "HET" represents a non-aromatic heterocyclic group; or

the other of R and R<sup>1</sup> represents a bicyclic heterocyclic group, composed of a 5 to 6 membered monocyclic heterocyclic group fused to a benzene ring, and

which bicyclic heterocyclic group may be substituted one or more times with

alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; alkoxy-alkoxy; cycloalkoxy; alkenoxy; alkynoxy; methylenedioxy; halogen; -OH; -CF<sub>3</sub>; -OCF<sub>3</sub>; -CN; amino; nitro; oxime; alkyloxime; or acyloxime;

an aryl group, which aryl group is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or acyloxime;

a monocyclic 5- to 6-membered heterocyclic group, which heterocyclic group is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or acyloxime; or

R and/or R<sup>1</sup>, together with the nitrogen atom to which they are attached, represent an alkyl-onium salt, a dialkyl-onium salt, a cycloalkyl-onium salt, an alkyl-cycloalkyl-onium salt, a dicycloalkyl-onium salt, an alkyl-cycloalkylalkyl-onium salt, a cycloalkyl-cycloalkylalkyl-onium salt, or a dicycloalkylalkyl-onium salt.

Moreover, the diazabicycloalkane derivative of the invention may be an enantiomer or a mixture of enantiomers, a pharmaceutically acceptable salt, and it may be provided in a labelled or un-labelled form.

In a preferred embodiment, the group bridging R and R<sup>1</sup> is a 3,9-diazabicyclo[4.2.1]nonane.

In another preferred embodiment, R and R<sup>1</sup> represents hydrogen or alkyl, and the other of R and R<sup>1</sup> represents a monocyclic 5- to 6-membered heterocyclic group, which heterocyclic group may be substituted with halogen, alkoxy, or alkenoxy.

In a third preferred embodiment, R or R<sup>1</sup> represents 6-chloro-3-pyridinyl, 5-(propyl-1-en-oxy)-3-pyridyl, 5-ethenyloxy-3-pyridyl, 5-ethoxy-3-pyridyl, or 5-methoxy-3-pyridyl.

In a most preferred embodiment, the diazabicycloalkane derivative of the invention is

3-[6-Chloro-(3-pyridazinyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-[6-Chloro-(3-pyridazinyl)]-3,9-diazabicyclo-[4.2.1]-nonane;  
3-[5-(Propyl-1-en-oxy)-3-pyridyl]-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(5-Ethenyloxy-3-pyridyl)-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(5-Ethoxy-3-pyridyl)-3,9-diazabicyclo-[4.2.1]-nonane;  
3-[5-Ethoxy-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-[5-(Propyl-1-en-oxy)-3-pyridyl]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(5-Ethenyloxy-3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
9-[5-Ethoxy-(3-pyridyl)]-3,9-diazabicyclo-[4.2.1]-nonane;  
9-[5-(Propyl-1-en-oxy)-(3-pyridyl)]-3,9-diazabicyclo-[4.2.1]-nonane;  
9-[5-Methoxy-(3-pyridyl)]-3,9-diazabicyclo-[4.2.1]-nonane;  
3-[6-Chloro-(3-pyridazinyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-[5-Bromo-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-[5-Chloro-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-[5-Bromo-(3-pyridyl)]-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-[5-Chloro-(3-pyridyl)]-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-[6-Bromo-5-ethoxy-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-[6-Chloro-5-ethoxy-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(3-Pyridyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-(3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(6-Bromo-3-pyridazinyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(6-Iodo-3-pyridazinyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(6-Bromo-3-pyridazinyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-(6-Iodo-3-pyridazinyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-(6-Chloro-3-Pyridyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-(6-Chloro-3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(6-Bromo-3-Pyridyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-(6-Bromo-3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(6-Fluoro-3-Pyridyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-(6-Fluoro-3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(6-Iodo-3-Pyridyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane; or  
3-(6-Iodo-3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
or a pharmaceutically acceptable addition salt thereof.

### 35 Definition of substituents

In the context of this invention halogen represents fluorine, chlorine, bromine or iodine.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably

5 contain of from one to eighteen carbon atoms (C<sub>1-18</sub>-alkyl), more preferred of from one to eight carbon atoms (C<sub>1-8</sub>-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C<sub>1-4</sub>-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another  
10 5 preferred embodiment of this invention alkyl represents a C<sub>1-3</sub>-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention an alkenyl group designates a carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a  
15 preferred embodiment the alkenyl group of the invention comprises of from two to eight carbon atoms (C<sub>2-8</sub>-alkenyl), more preferred of from two to six carbon atoms (C<sub>2-6</sub>-alkenyl), including at least one double bond. In a most preferred embodiment the alkenyl group of the invention is ethenyl; 1- or 2-propenyl; 1-, 2- or 3-butenyl, or 1,3-  
20 butenyl; 1-, 2-, 3-, 4- or 5-hexenyl, or 1,3-hexenyl, or 1,3,5-hexenyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-octenyl, or 1,3-octenyl, or 1,3,5-octenyl, or 1,3,5,7-octenyl.

15 In the context of this invention an alkynyl group designates a carbon chain containing one or more triple bonds, including di-yne, tri-yne and poly-yne. In a preferred embodiment the alkynyl group of the invention comprises of from two to eight carbon atoms (C<sub>2-8</sub>-alkynyl), more preferred of from two to six carbon atoms (C<sub>2-6</sub>-alkynyl), including at least one triple bond. In its most preferred embodiment the  
20 alkynyl group of the invention is ethynyl; 1-, or 2-propynyl; 1-, 2-, or 3-butynyl, or 1,3-butynyl; 1-, 2-, 3-, 4-pentynyl, or 1,3-pentynyl; 1-, 2-, 3-, 4-, or 5-hexynyl, or 1,3-hexynyl or 1,3,5-hexynyl; 1-, 2-, 3-, 4-, 5- or 6-heptynyl, or 1,3-heptynyl, or 1,3,5-heptynyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-octynyl, or 1,3-octynyl, or 1,3,5-octynyl, or 1,3,5,7-octynyl.

25 In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C<sub>3-7</sub>-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the context of this invention a cycloalkyl-alkyl group designates a  
40 cycloalkyl group as defined above, which cycloalkyl group is substituted on an alkyl group as also defined above. Examples of preferred cycloalkyl-alkyl groups of the invention include cyclopropylmethyl and cyclopropylethyl.

In the context of this invention an alkoxy group designates an "alkyl-O-"  
45 group, wherein alkyl is as defined above, an alkenoxy group designates an "alkenyl-O-" group, wherein alkenyl is as defined above, and a cycloalkoxy group designates a "cycloalkyl-O-" group, wherein cycloalkyl is as defined above.  
35

In the context of this invention an alkylthio group designates an "alkyl-S-"  
50 group (thioalkoxy), wherein alkyl is as defined above, an alkenylthio group designates an "alkenyl-S-" group, wherein alkenyl is as defined above, and an alkynylthio group designates an "alkynyl-S-" group, wherein alkynyl is as defined above. Likewise an

5 arylthio group designates an "aryl-S-" group, wherein aryl is as defined below, and an arylalkylthio designates an "arylalkyl-S-" group, wherein arylalkyl is as defined below, alkylthio-alkoxy, alkoxy-alkylthio, and alkylthio-alkylthio designates an alkylthio group as defined above, attached to another alkylthio group, or to an alkoxy group as

10 defined above.

In the context of this invention an alkylseleno group designates an "alkyl-Se-" group, wherein alkyl is as defined above, an alkenylseleno designates an "alkenyl-Se-" group, wherein alkenyl is as defined above, and an alkynylseleno group designates an "alkynyl-Se-" group, wherein alkynyl is as defined above.

15 In the context of this invention an alkylloxime group designates a "C=N-O-alkyl" group, wherein alkyl is as defined above, and an acyloxime group designates a "C=N-O-COOH" group or a "C=N-O-CO-alkyl" group, wherein alkyl is as defined above.

20 In the context of this invention an amino group may be a primary (-NH<sub>2</sub>), secondary (-NH-alkyl), or tertiary (-N(alkyl)<sub>2</sub>) amino group, i.e. it may be substituted once or twice with an alkyl group as defined above.

25 In the context of this invention aryl designates a mono- or polycyclic aryl group, i.e. a monocyclic or polycyclic aromatic hydrocarbon group. Examples of preferred aryl groups of the invention include phenyl, naphthyl, indenyl, azulenyl, anthracenyl, and fluorenyl.

30 In the context of this invention an aralkyl group designates a mono- or polycyclic aryl group as defined above, which aryl group is attached to an alkyl group as also defined above. Examples of preferred aralkyl groups of the invention include benzyl, and phenethyl.

35 In the context of this invention a monocyclic heterocyclic group is a monocyclic compound, which holds one or more heteroatoms in its ring structure. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S). The ring structure may in particular be aromatic (i.e. a heteroaryl), or saturated or partially saturated ("HET"). Preferred heterocyclic monocyclic groups of the invention include

40 5- and 6 membered heterocyclic monocyclic groups.  
Examples of preferred aromatic heterocyclic 5-membered monocyclic groups of the invention include

45 furan, in particular 2- or 3-furanyl;

thiophene, in particular 2- or 3-thienyl;

35 pyrrole, in particular 1-, 2- or 3-pyrrolyl;

oxazole, in particular oxazol-(2-,4- or 5-)yl;

thiazole, in particular thiazol-(2-,4-, or 5-)yl;

50 imidazole, in particular imidazol-(1-,2-,4- or 5-)yl;

pyrazole, in particular pyrazol-(1-,3-,4- or 5-)yl;

isoxazol , in particular isoxazol-(3-,4- or 5-)yl;  
isothiazole, in particular isothiazol-(3-,4- or 5-)yl;  
1,2,3-oxadiazole, in particular 1,2,3-oxadiazol-(4- or 5-)yl;  
1,2,4-oxadiazole, in particular 1,2,4-oxadiazol-(3- or 5-)yl;  
1,2,5-oxadiazole, in particular 1,2,5-oxadiazol-(3- or 4-)yl;  
1,2,3-triazole, in particular 1,2,3-triazol-(1-,4- or 5-)yl;  
1,2,4-thiadiazole, in particular 1,2,4-thiadiazol-(3- or 5-)yl;  
1,2,5-thiadiazole, in particular 1,2,5-thiadiazol-(3- or 4-)yl; and  
1,3,4-thiadiazole, in particular 1,3,4-thiadiazol-(2- or 5-)yl.

Examples of preferred aromatic heterocyclic 6-membered monocyclic groups of the invention include

pyridine, in particular pyridin-(2-,3- or 4-)yl;  
pyridazine, in particular pyridazin-(3- or 4-)yl;  
pyrimidine, in particular pyrimidin-(2-,4- or 5-)yl;  
pyrazine, in particular pyrazin-(2- or 3-)yl;  
1,3,5-triazine, in particular 1,3,5-triazin-(2-,4- or 6-)yl; and  
phosphinine, in particular phosphinin-(2-,3- or 4-)yl.

In the context of this invention a bicyclic heterocyclic group is a bicyclic compound composed of a monocyclic 5 to 6 membered heterocyclic group as described above, which heterocyclic group is fused to a benzene ring.

Examples of preferred aromatic heterocyclic bi-cyclic groups of the invention include

indolizine, in particular indolizin-(1-,2-,3-,5-,6-,7- or 8-)yl;  
indole, in particular indol-(1-,2-,3-,4-,5-,6- or 7-)yl;  
isoindole, in particular isoindol-(1-,2-,3-,4-,5-,6- or 7-)yl;  
benzo[b]furan (benzofuran), in particular benzo[b]furan-(2-,3-,4-,5-,6- or 7-)yl;  
benzo[c]furan (isobenzofuran), in particular benzo[c]furan-(1-,3-,4-,5-,6- or 7-)yl;  
benzo[b]thiophene (benzothiophene), in particular benzo[b]thiophen-(2-,3-,4-,5-,6- or 7-)yl;  
benzo[c]thiophene (isobenzothiophene), in particular benzo[c]thiophen-(1-,3-,4-,5-,6- or 7-)yl;  
benzimidazole, in particular benzimidazol-(1-,2-,4-,5-,6- or 7-)yl;  
benzthiazole, in particular benzthiazol-(2-,4-,5-,6- or 7-)yl;  
purine, in particular purin-(2-,6- or 8-)yl;  
quinoline, in particular quinolin-(2-,3-,4-,5-,6-,7- or 8-)yl;  
isoquinoline, in particular isoquinolin-(1-,3-,4-,5-,6-,7- or 8-)yl;  
cinnoline, in particular cinnolin-(3-,4-,5-,6-,7- or 8-)yl;  
phthlazine, in particular phthlazin-(1-,4-,5-,6-,7- or 8-)yl;  
quinazoline, in particular quinazolin-(2-,4-,5-,6-,7- or 8-)yl;

quinoxaline, in particular quinoxalin-(2-,3-,5-,6-,7- or 8-)yl;  
1,8-naphthyridine, in particular 1,8-naphthyridin-(2-,3-,4-,5-,6- or 7-)yl; and  
pteridine, in particular pteridin-(2-,4-,6- or 7-)yl.

Examples of preferred saturated or partially saturated heterocyclic bi-cyclic

groups of the invention include

indoline, in particular indolin-(1-,2-,3-,4-,5-,6- or 7-)yl;  
3H-indole, in particular 3H-indol-(2-,3-,4-,5-,6- or 7-)yl;  
1H-indazole, in particular 1H-indazol-(3-,4-,5-,6- or 7-)yl;  
4H-quinolizine, in particular 4H-quinolizin-(1-,2-,3-,4-,6-,7-,8- or 9-)yl;  
quinuclidine, in particular quinuclidin-(2-,3-,4-,5-,6-,7- or 8-)yl;  
isoquinuclidine, in particular isoquinuclidin-(1-,2-,3-,4-,5-,6-,7- or 8-)yl;  
tropane, in particular tropan-(1-,2-,3-,4-,5-,6-,7- or 8-)yl; and  
nortropane, in particular nortropan-(1-,2-,3-,4-,5-,6- or 7-)yl.

In the context of this invention "HET" represents a non-aromatic (i.e.  
saturated or partially saturated) monocyclic heterocyclic group containing at least one  
heteroatom. Preferred

Examples of preferred non-aromatic heterocyclic monocyclic 3- or 4-  
membered groups of the invention include aziridine; azetidine; and azacyclobutene;

Examples of preferred non-aromatic heterocyclic monocyclic 5-membered  
groups of the invention include

2H-pyrrole, in particular 2H-pyrrol-(2- or 3-)yl;  
3H-pyrrole, in particular 3H-pyrrol-(2- or 3-)yl;  
2,3-dihydro-pyrrole, in particular 2,3-dihydro-pyrrol-(2- or 3-)yl;  
3,4-dihydro-pyrrole, in particular 3,4-dihydro-pyrrol-(2- or 3-)yl;  
2-pyrroline, in particular 2-pyrrolin-(1-,2- or 3-)yl;  
3-pyrroline, in particular 3-pyrrolin-(1-,2- or 3-)yl;  
pyrrolidine, in particular pyrrolidin-(1-,2- or 3-)yl;  
1,3-dioxolan, in particular 1,3-dioxolan-(2- or 4-)yl;  
imidazolidine, in particular imidazolidin-(1-,2-,3-,4- or 5-)yl;  
2-imidazoline, in particular 2-imidazolin-(1-,2-,4- or 5-)yl;  
3-imidazoline, in particular 3-imidazolin-(1-,2-,4- or 5-)yl;  
4-imidazoline, in particular 4-imidazolin-(1-,2-,4- or 5-)yl;  
pyrazolidine, in particular pyrazolidin-(1-,2-,3-,4- or 5-)yl;  
2-pyrazoline, in particular 2-pyrazolin-(1-,3-,4- or 5-)yl; and  
3-pyrazoline, in particular 3-pyrazolin-(1-,3-,4- or 5-)yl.

Examples of preferred non-aromatic heterocyclic monocyclic 6-membered  
groups of the invention include

2,3-dihydropyridine, in particular 2,3-dihydropyridin-(2-,3- or 4-)yl;  
3,4-dihydropyridine, in particular 3,4-dihydropyridin-(2-,3- or 4-)yl;

5 4,5-dihydropyridine, in particular 4,5-dihydropyridin-(2-,3- or 4-)yl;  
5,6-dihydropyridine, in particular 5,6-dihydropyridin-(2-,3- or 4-)yl;  
tetrahydropyridine, in particular tetrahydropyridin-(2-,3- or 4-)yl;  
2H-pyran, in particular 2H-pyran-(2-,3- or 4-)yl;  
10 5 4H-pyran, in particular 4H-pyran-(2-,3- or 4-)yl;  
piperidine, in particular piperidin-(1-,2-,3- or 4-)yl;  
1,4-dioxolane, in particular 1,4-dioxolan-(2- or 3-)yl;  
morpholine, in particular morpholin-(2-,3- or 4-)yl;  
15 1,4-dithiane, in particular 1,4-dithian-(2- or 3-)yl;  
10 thiomorpholine, in particular thiomorpholin-(2-,3- or 4-)yl;  
piperazine, in particular piperazin-(1-,2-,3- or 4-)yl;  
1,3,5-trithiane, in particular 1,3,5-trithian-(2-)yl;  
20 1,4-oxazine, in particular 1,4-oxazin-(2-)yl; and  
morpholine, in particular morpholin-(2- or 3-)yl;

15 Examples of preferred non-aromatic heterocyclic monocyclic 7- to 8-  
membered groups of the invention include homopiperidine; homopiperazine;  
25 azacyclooctane; and diazacyclooctane.

#### Pharmaceutically Acceptable Salts

20 The chemical compound of the invention may be provided in any form  
suitable for the intended administration. Suitable forms include pharmaceutically (i.e.  
30 physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound  
of the invention.

Examples of pharmaceutically acceptable addition salts include, without  
35 limitation, the non-toxic inorganic and organic acid addition salts such as the  
hydrochloride derived from hydrochloric acid, the hydrobromide derived from  
hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from  
perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived  
40 from sulphuric acid, the formate derived from formic acid, the acetate derived from  
30 acetic acid, the aconate derived from aconitic acid, the ascorbate derived from  
ascorbic acid, the benzenesulphonate derived from benzenesulphonic acid, the  
benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the  
citrate derived from citric acid, the embonate derived from embonic acid, the enantate  
45 derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate  
35 derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived  
from lactic acid, the maleate derived from maleic acid, the malonate derived from  
malonic acid, the mandelate derived from mandelic acid, the methanesulphonate  
50 derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from  
naphthalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate



5 derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

10 5 Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

15 Metal salts of a chemical compound of the invention includes alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

20 In the context of this invention the "onium salts" of N- and/or S-containing compounds are also contemplated as pharmaceutically acceptable salts. Preferred "onium salts" include the alkyl-onium salts, the cycloalkyl-onium salts, and the 15 cycloalkylalkyl-onium salts.

25 The chemical compound of the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvents such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, 20 and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

#### Labelled Compounds

35 The compounds of the invention may be used in their labelled or unlabelled form. In the context of this invention "label" stands for the binding of a marker to the compound of interest that will allow easy quantitative detection of said compound.

40 The compounds of the invention may be useful as diagnostic tools, radio tracers, or monitoring agents in various diagnostic methods, and in particular for *in vivo* receptor imaging, where they are preferably employed in labelled form.

30 In the context of this invention an isotopes designates a labelled compound in which one or more atoms has been changed into an isotope of the naturally occurring atom. Labelled compounds and includes though not limited to  $^2\text{H}$  (deuterium),  $^3\text{H}$  (tritium),  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{18}\text{F}$ , as described in more details below (under "neuroimaging").

#### Steric Isomers

50 It will be appreciated by those skilled in the art that the compounds of the present invention may contain one or more chiral centres, and that such compounds

5 exist in the form of isomers (i. . . enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual  
10 5 isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by  
15 treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or  
20 camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by  
15 the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by  
25 the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

20 Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

25 Moreover, some of the chemical compounds of the invention being oximes, may thus exist in two forms, syn- and anti-form (Z- and E-form), depending on the arrangement of the substituents around the -C=N- double bond. A chemical compound of the present invention may thus be the syn- or the anti-form (Z- and E-  
30 form), or it may be a mixture hereof.

### 30 **Methods of Producing Diazabicycloalkane Derivatives**

The diazabicycloalkane derivatives of the invention may be prepared by  
45 conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present  
35 application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another  
50 compound of the invention using conventional methods.

5 The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

## 10 5 Biological Activity

The diazabicycloalkane derivatives of the present invention are nicotinic receptor modulators. In the context of this invention the term "modulator" covers agonists, partial agonists, antagonists and allosteric modulators of the nicotinic acetylcholine receptor (nAChR).

15 The compounds of the present invention exhibit a nicotinic pharmacology at least as good as nicotine itself, but preferably with lesser or even without the side effects associated with the use of nicotine. Moreover, the compounds of the invention are believed to have the potential as enhancers of neurotransmitter secretion, and suppress symptoms associated with a low activity of neurotransmitters.

20 The compounds of the present invention may in particular be characterised by having one or more of the following functionalities: A high binding selectivity for the receptor subtypes of neuronal nAChR's, in particular the  $\alpha 3$  and/or the  $\alpha 7$  subtype, binding selectivity for the serotonin receptor, a low affinity for the muscular subtype, an induction of cell survival, an oral efficacy *in vivo* of arousal/attention, a low toxicity *in vivo*, and by being non-mutagenic.

30 Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or conditions as diverse as CNS related diseases, diseases related to smooth muscle contraction, endocrine disorders, diseases related to neurodegeneration, diseases related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

35 In a preferred embodiment the compounds of the invention are used for the treatment of diseases, disorders, or conditions relating to the central nervous system. Such diseases or disorders includes anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, chronic fatigue syndrome, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

5 In another preferred embodiment the compounds of the invention may be useful for the treatment of diseases, disorders, or conditions associated with smooth muscle contractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia,  
10 5 premature ejaculation, and erectile difficulty.

In yet another preferred embodiment the compounds of the invention may be useful for the treatment of endocrine disorders, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

15 In still another preferred embodiment the compounds of the invention may be useful for the treatment of neurodegenerative disorders, including transient anoxia and induced neurodegeneration.

20 In even another preferred embodiment the compounds of the invention may be useful for the treatment of inflammatory diseases, disorders, or conditions, including inflammatory skin disorders such as acne and rosacea, Chron's disease,  
15 inflammatory bowel disease, ulcerative colitis, and diarrhoea.

25 In still another preferred embodiment the compounds of the invention may be useful for the treatment of mild, moderate or even severe pain of acute, chronic or recurrent character, as well as pain caused by migraine, postoperative pain, and phantom limb pain.

20 Finally the compounds of the invention may be useful for the treatment of withdrawal symptoms caused by termination of use of addictive substances. Such  
30 addictive substances include nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol. Withdrawal from addictive substances is in general a traumatic  
35 experience characterised by anxiety and frustration, anger, anxiety, difficulties in concentrating, restlessness, decreased heart rate and increased appetite and weight gain.

40 In this context "treatment" covers treatment, prevention, prophylactics and alleviation of withdrawal symptoms and abstinence as well as treatment resulting in a  
30 voluntary diminished intake of the addictive substance.

45 In another aspect, the compounds of the invention are used as diagnostic agents, e.g. for the identification and localisation of nicotinic receptors in various tissues. For this purpose the stannate derivatives of the are particularly useful.

### 35 Neuroimaging

50 The diazabicycloalkane derivatives of the invention, in particular those being selective for the nicotinic receptor subtype  $\alpha 3$ , may be useful as diagnostic tools or monitoring agents in various diagnostic methods, and in particular for *in vivo* receptor imaging (neuroimaging).

5 In another aspect of the invention, a method for the non-invasive determination of the distribution of a tracer compound inside a whole, intact living animal or human body using a physical detection method is provided. According to this method a tracer compound is a compound of the invention, or any of its  
10 5 enantiomers or any mixture thereof, an N oxide thereof, a pharmaceutically acceptable salt thereof, in a labelled or un-labelled form.

In a preferred embodiment the physical detection method is selected from PET, SPECT; MRS, MRI, CAT, or combinations thereof.

15 The labelled compound of the invention preferably contains at least one radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In the context of this invention the radionuclide is preferably selected from  $^2\text{H}$  (deuterium),  $^3\text{H}$  (tritium),  $^{11}\text{C}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{O}$ ,  $^{13}\text{N}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{18}\text{F}$  and  $^{99\text{m}}\text{Tc}$ .  
20

An examples of commercially available labelling agents, which can be used in the preparation of the labelled compounds of the present invention is  $^{11}\text{C}]\text{O}_2$ ,  $^{18}\text{F}$ ,  
15 and NaI with different isotopes of Iodine.

In particular  $^{11}\text{C}]\text{O}_2$  may be converted to a  $^{11}\text{C}$ ]-methylating agent, such as  $^{11}\text{C}]\text{H}_3\text{I}$  or  $^{11}\text{C}$ ]-methyl triflate.

25 Labelled compounds containing e.g.  $^{125}\text{I}$  labelled 1-iodoprop-1-en-3-yl as substituent on N-8 may be prepared as described in the art [*Elmaleh, et al.*; J. Nucl. Med. 1996 **37** 1197-1202].  
20

30 Labelled compounds containing e.g.  $^{18}\text{F}$ ]-alkyl substituted N-8 may be prepared as described in the art, e.g. in WO 96/39198.

The tracer compound can be selected in accordance with the detection method chosen.

35 25 In one preferred embodiment, the labelled or unlabelled compound of the invention can be detected by a suitable spectroscopic method, in particular UV spectroscopy and/or fluorescence spectroscopy.

40 In another preferred embodiment, the compounds of the invention labelled by incorporation of a isotope into the molecule, which may in particular be an isotope  
30 of the naturally occurring atoms including  $^2\text{H}$  (deuterium),  $^3\text{H}$  (tritium),  $^{11}\text{C}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{O}$ ,  $^{13}\text{N}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{18}\text{F}$  and  $^{99\text{m}}\text{Tc}$ , and the isotope incorporation may be measured by conventional scintillation counting techniques.

45 In a third preferred embodiment, the physical method for detecting said tracer compound of the present invention is selected from Position Emission  
35 Tomography (PET), Single Photon Imaging Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT), or combinations thereof.  
50

5 Before conducting the method of the present invention, a diagnostically effective amount of a labelled or unlabelled compound of the invention is administered to a living body, including a human.

10 The diagnostically effective amount of the labelled or unlabelled compound of the invention to be administered before conducting the in-vivo method for the present invention is within a range of from 0.1 ng to 100 mg per kg body weight, preferably within a range of from 1 ng to 10 mg per kg body weight.

### 15 **Pharmaceutical Compositions**

10 In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the chemical compound of the invention.

20 While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

25 In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefor, and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

35 25 Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or 40 30 insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semi-permeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or 45 microcapsules.

35 35 The chemical compound of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular 50 tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the

5 same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may  
10 5 contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The chemical compound of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either  
15 10 a chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from a chemical compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets,  
20 15 suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the  
20 finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about  
35 25 seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the  
40 30 active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty  
45 35 acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

5 Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

10 Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

15 The chemical compound according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient 20 may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

25 Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

30 Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

35 Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the 40 like.

45 For topical administration to the epidermis the chemical compound of the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be 35 formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

50 Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia



5 or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

10 Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump.

15 Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant 20 such as lecithin. The dose of drug may be controlled by provision of a metered valve.

25 Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal 30 cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

35 In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

40 The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as 45 packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate 35 number of any of these in packaged form.

50 Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

A therapeutically effective dose refers to that amount of active ingredient which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED<sub>50</sub> and LD<sub>50</sub>, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD<sub>50</sub>/ED<sub>50</sub>. Pharmaceutical compositions which exhibit large therapeutic indexes are preferred.

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The actual dosage depend on the nature and severity of the disease being treated and the route of administration, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

#### Methods of Therapy

The compounds of the present invention are valuable nAChR modulators and therefore useful for the treatment of a range of ailments involving cholinergic dysfunction as well as a range of disorders responsive to the action of nAChR modulators as well as the serotonin receptor.

In another aspect the invention relates to the a method of the treatment or alleviation of a disease, disorder or condition of a living animal body, including a human, which disease, disorder or condition is responsive to the action of a nicotinic Acetyl Choline Receptor (nAChR) modulator, which method comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of the chemical compound of the invention.

5 In the context of this invention the term "treating" covers treatment, prevention, prophylaxis or alleviation, and the term "disease" covers illnesses, diseases, disorders and conditions related to the disease in question.

10 In a preferred embodiment the disease or disorder to be treated is a disease or disorder of the central nervous system, a disease or disorder caused by or related to smooth muscle contraction, an endocrine disorder, a disease or disorder caused by or related to neuro-degeneration, a disease or disorder caused by or related to inflammation, pain, a withdrawal symptom caused by the termination of abuse of chemical substances.

15 In a more preferred embodiment the disease or disorder of the central nervous system is anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, depression, mania, manic depression, 20 schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, chronic fatigue syndrome, sleeping disorders, pseudodementia, Ganser's syndrome, 25 pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

30 In another preferred embodiment the disease or disorder caused by or related to smooth muscle contraction is convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, 35 hyperkinesia, premature ejaculation, and erectile difficulty.

40 In a third preferred embodiment the endocrine disorder is thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

45 In a fourth preferred embodiment the neuro-degenerative disease is transient anoxia and induced neurodegeneration.

50 In a fifth preferred embodiment the disease or disorder caused by or related to inflammation is an inflammatory skin disorder such as acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

55 In a sixth preferred embodiment pain is a mild, a moderate or a severe pain of acute, chronic or recurrent character, a pain caused by migraine, a postoperative pain, or a phantom limb pain.

In a third preferred embodiment the addictive substance is a nicotine containing product such as tobacco, an opioids such as heroin, cocaine or morphine, a benzodiazepine or a benzodiazepine-like drug, or alcohol.

5 It is at present contemplated that a suitable dosage lies within the range of  
from about 0.1 to about 500 milligram of active substance daily, more preferred of  
from about 10 to about 70 milligram of active substance daily, administered once or  
10 twice a day, dependent as usual upon the exact mode of administration, form in which  
5 administered, the indication toward which the administration is directed, the subject  
involved and the body weight of the subject involved, and further the preference and  
experience of the physician or veterinarian in charge.

## 15 EXAMPLES

10 The invention is further illustrated in the following examples which are not  
intended to be in any way limiting to the scope of the invention as claimed.

20 All reactions involving air sensitive reagents or intermediates were  
performed under nitrogen and in anhydrous solvents. Magnesium sulphate is used as  
15 drying agent in the workup-procedures and solvents were evaporated under reduced  
pressure.

### 25 Example 1

#### 20 Preparatory Examples

##### 30 9-Methyl-3,9-diazabicyclo-[4.2.1]-nonane

was prepared according to [Michaels RJ and Zaugg HE; J. Org. Chem. 1960 **25** 637].

##### 25 3-Chloro-5-ethoxyloxy-pyridine

35 Thionyl chloride (58.6 g, 493 mmol) was added to a mixture of 3-chloro-5-(2-  
hydroxyethoxy)pyridine (14.5 g, 82.1 mmol) and tetrahydrofuran (100 ml). The mixture  
was stirred for 1 h at 50 °C. The mixture was evaporated. Potassium hydroxide (9.0 g,  
164 mmol) and *tert*-butanol (100 ml) were added and the mixture was stirred for 3  
40 30 days at 100 °C. The solvent was evaporated. Water (150 ml) was added and the  
mixture was extracted twice with diethyl ether (100 ml). Yield 6.77 g, 53%.

##### 3-Chloro-5-(2-hydroxyethoxy)-pyridine

45 A mixture of sodium (2.0 g, 89.5 mmol) and ethylene glycol (50 ml) was stirred at  
35 70°C for 30 min. 3,5-Dichloropyridine (11.0 g, 74.5 mmol) and dimethyl sulfoxide (50  
ml) were added to the crude mixture. The crude mixture was stirred for 10 h at 110 °C.  
Aqueous sodium hydroxide (100 ml) was added and the crystals were filtered. Yield  
50 8.0 g, 51%.

##### 40 3-Chloro-5-ethoxy-pyridine

Sodium (8.1 g, 338 mmol) was added to ethanol (200 ml). After complete reaction, the excess of ethanol was evaporated. 3,5-Dichloropyridine (40.0 g, 270 mmol) and dimethyl sulfoxide (300 ml) were added to the crude mixture. The mixture was stirred at 70 °C for 1 h. Water (500 ml) was added, followed by extraction twice with ethyl acetate (300 ml). The product was isolated in quantitative yield.

3-Allyloxy-5-chloropyridine

Sodium (4.7 g, 203 mmol) was added to allyl alcohol (57.5 ml, 84.5 mmol). After complete reaction, the excess of allyl alcohol was evaporated. 3,5-Dichloropyridine (25.0 g, 169 mmol) and dimethyl sulfoxide (75 ml) were added to the crude mixture. The mixture was stirred at 60 °C overnight. Water (100 ml) was added followed by extraction twice with ethyl acetate (100 ml). The product was isolated in quantitative yield.

**Method A**

3-[6-Chloro-(3-pyridazinyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt (Compound 1A1)

A mixture of 9-methyl-3,9-diazabicyclo-[4.2.1]-nonane (0.50 g, 3.6 mmol), 3,6-dichloropyridazine (0.53 g, 3.6 mmol) and toluene (20 ml) was stirred at reflux for 2.5 h. Aqueous sodium hydroxide (20 ml, 1 M) was added. The mixture was extracted three times with ethyl acetate (20 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 0.32 g, 24%. Mp. 196-198°C.

**Method B**

3-[6-Chloro-(3-pyridazinyl)]-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt (Compound 1B1)

A mixture of 3-[6-chloro-(3-pyridazinyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane (0.5 g, 2.0 mmol), diethyl azodicarboxylate (1.72 g, 9.9 mmol) and toluene (15 ml) was stirred at reflux for 1 h. Aqueous hydrochloric acid (10 ml, 4 M) was added, followed by stirring for 5 min. Aqueous sodium hydroxide (15 ml, 4 M) was added, and the mixture was extracted three times with ethyl acetate (30 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 50 mg, 7%. Mp. 172-174°C.

3-[5-(Propyl-1-en-oxy)-3-pyridyl]-3,9-diazabicyclo-[4.2.1]-nonane bis fumaric acid salt (Compound 1B2)

Prepared according to method B. Mp. 144-146°C.

3-(5-Ethenyloxy-3-pyridyl)-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt  
(Compound 1B3)

Prepared according to method B. Mp. 145-147°C.

3-(5-Ethoxy-3-pyridyl)-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt (Compound 1B4)

Prepared according to method B. Mp. 143-146°C.

**Method C**

3-[5-Ethoxy-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane bis-fumaric acid salt  
(Compound 1C1)

A mixture of 9-methyl-3,9-diazabicyclo-[4.2.1]-nonane (1.50 g, 10.7 mmol), 3-chloro-5-ethoxypyridine (3.38 g, 21.4 mmol), potassium *tert*-butoxide (2.4 g, 21.4 mmol) and 1,2-dimethoxyethane (20 ml) was stirred at room temperature overnight. Aqueous sodium hydroxide (30 ml, 1 M) was added and the mixture was extracted two times with ethyl acetate (20 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 0.39 g, 21%. Mp. 142-144°C.

3-[5-(Propyl-1-en-oxy)-3-pyridyl]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt  
(Compound 1C2)

Prepared according to method C from 3-allyloxy-5-chloropyridine, involving a complete isomerization of the double bond. Mp. 132-134°C.

3-(5-Ethenyloxy-3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt  
(Compound 1C3)

Prepared according to method C from 3-chloro-5-ethenyloxy-pyridine. Mp. 151-153°C.

**Method D**

9-[5-Ethoxy-(3-pyridyl)]-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt  
(Compound 1D1)

A mixture of 9-[5-ethoxy-(3-pyridyl)]-3-*tert*-butoxycarbonyl-3,9-diazabicyclo-[4.2.1]-nonane (0.23 g, 0.66 mmol), trifluoroacetic acid (0.75 g, 6.6 mmol) and dichloromethane (10 ml) was stirred for 3 days at room temperature. Sodium hydroxide (20 ml, 1M) was added and the phases were separated, followed by extraction with dichloromethane (20 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound.

The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 0.39 g, 21%. Mp. 191-192°C.

9-[5-(Propyl-1-en-oxy)-(3-pyridyl)]-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt

5 (Compound 1D2)

Was prepared according to method D. Mp. 161.5-163.0°C.

9-[5-Methoxy-(3-pyridyl)]-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt

15 (Compound 1D3)

10 Was prepared according to method D. Mp. 183-185°C.

**Method E**

9-[5-Ethoxy-(3-pyridyl)]-3-*tert*-butoxycarbonyl-3,9-diazabicyclo-[4.2.1]-nonane

20 (Compound 1E1)

15 A mixture of 3-*tert*-butoxycarbonyl-3,9-diazabicyclo-[4.2.1]-nonane (1.1 g, 4.9 mmol), 3-chloro-5-ethoxypyridine (0.77 g, 4.9 mmol), potassium-*tert*-butoxide (1.09 g, 9.7 mmol) and 1,2-dimethoxyethane (20 ml) was heated at reflux for 1.5 h. Sodium hydroxide (30 ml, 1 M) was added and the aqueous phase was extracted twice with ethyl acetate (30 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as an oil. Yield 0.24 g, 14%.

30 3-*Tert*-butoxycarbonyl-3,9-diazabicyclo-[4.2.1]-nonane (Compound 1E2)

9-Methyl-3-*tert*-butoxycarbonyl-3,9-diazabicyclo-[4.2.1]-nonane (3.4 g, 14.1 mmol), Diethylazodicarboxylate (12.3 g, 70.7 mmol) and toluene (35 ml) was stirred at reflux for 1.5 h. Sodiumhydroxide (50 ml, 1 M) was added. The aqueous phase was extracted twice with ethyl acetate (50 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as an oil. Yield 1.13 g, 35%.

40 9-Methyl-3-*tert*-butoxycarbonyl-3,9-diazabicyclo-[4.2.1]-nonane (Compound 1E3)

45 A mixture of 9-Methyl-3,9-diazabicyclo-[4.2.1]-nonane (2.0 g, 14.3 mmol), triethylamine (2.89 g, 28.6 mmol), Di-*tert*-butyl-dicarbonate (3.12 g, 14.3 mmol) and dichloromethane (20 ml) was stirred overnight at room temperature. Sodium hydroxide (30 ml, 1 M) was added. The phases were separated and the aqueous phase was extracted with dichloromethane (30 ml). The title compound was isolated as an oil. Yield 3.5 g.

**Method F****3-[5-Bromo-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt (Compound 1F1)**

A mixture of 3,5-dibromopyridine (25.0 g, 105 mmol) and of 9-methyl-3,9-diazabicyclo-[4.2.1]-nonane (14.8 g, 105 mmol), Palladium(dppp) (0.20 mg, 0.21 mmol) (prepared according to W. A. Hermann Angew Chem. Int. Ed Engl. 39, 1844, 1995) and dimethyl formamide (15 ml) was stirred for 3 days at 140°C. Aqueous sodium hydroxide (100 ml, 1 M) was added at room temperature. The mixture was extracted twice with ethyl acetate (2 x 100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as an oil. Yield 3.77 g (12%). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp. 173.5-175.5°C.

**3-[5-Chloro-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt (Compound 1F2)**

Was prepared according to method F. Mp. 181-182°C.

**3-[5-Bromo-(3-pyridyl)]-10-methyl-3,10-diazabicyclo-[4.3.1]-decane fumaric acid salt (Compound 1F3)**

Was prepared according to method F. Mp. 162.5-164.5°C.

**3-[5-Chloro-(3-pyridyl)]-10-methyl-3,10-diazabicyclo-[4.3.1]-decane fumaric acid salt (Compound 1F4)**

Was prepared according to method F. Mp. 152-153°C.

**Method G****3-[6-Bromo-5-ethoxy-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt****(Compound 1G1)**

A mixture of 3-[5-ethoxy-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane (0.53 g, 2.0 mmol) and N-bromosuccinimide (0.34 g, 1.9 mmol) and acetonitrile (20 ml) was stirred for 3 h at room temperature. The crude mixture was evaporated. Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the free base as an oil. Yield 98% (0.63 g). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid Mp. 177.4°C.

**3-[6-Chloro-5-ethoxy-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt**



**(Compound 1G2)**

Was prepared according to method G. Mp. 208.6°C.

**Method H****3-(3-Pyridyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane fumaric acid salt (Compound 1H1)**

A mixture of 3-fluoropyridine (8.74 g, 90 mmol) and 10-methyl-3,10-diazabicyclo-[4.3.1]-decane (13.9 g, 90 mmol) was stirred at 180 °C for 48 h. Aqueous sodium hydroxide (50 ml, 1M) was added at room temperature and the mixture was extracted with diethyl ether (2 x100 ml). Purification by column chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) yielded 26% of the free base (5,5 g, 24 mmol) as an oil, which was converted to the corresponding fumaric acid salt. Mp. 144.4-154.4°C.

**3-(3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt (Compound 1H2)**

Was prepared according to method H from 9-methyl-3,9-diazabicyclo-[4.2.1]-nonane. Mp. 170-172°C.

**Method I****3-(6-Bromo-3-pyridazinyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt (Compound 1I1)**

A mixture of 3,6-dibromopyridazine (1.0 g, 4.2 mmol), 9-methyl-3,9-diazabicyclo-[4.2.1]-nonane (0.59 g, 4.2 mmol) and diisopropylethylamine (1.5 ml, 8.4 mmol) was heated to reflux for 3 h. Aqueous sodium hydroxide (50 ml) was added and the mixture was extracted with diethyl ether (3 x 50 ml). Purification by column chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) afforded 68% of the product as free base. Yield 68% (0.85 g, 2.9 mmol) The free base was converted to the corresponding fumaric acid salt. Mp. 175.6°C.

**3-(6-Iodo-3-pyridazinyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane fumaric acid salt (Compound 1I2)**

Was prepared according to method I from 9-methyl-3,9-diazabicyclo-[4.2.1]-nonane and 3,6-diiodopyridazine. Mp. 163.2-167.0°C.

**3-(6-Bromo-3-pyridazinyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane fumaric acid salt (Compound 1I3)**

Was prepared according to method I from 10-methyl-3,10-diazabicyclo-[4.3.1]-decane. Mp. 178.1°C.

5 3-(6-Iodo-3-pyridazinyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane fumaric acid salt  
(Compound 114)

Was prepared according to method I from 10-methyl-3,10-diazabicyclo-[4.3.1]-decane. Mp. 162.5-166°C.

10 **Example 2**

**Biological Activity**

Nicotinic acetyl choline receptors in the brain are pentameric structures composed of subunits distinct from those found in skeletal muscles. The existence of seven  $\alpha$ -subunits ( $\alpha 2$ - $\alpha 7$ ,  $\alpha 9$ ) and three  $\beta$ -subunits ( $\beta 2$ - $\beta 4$ ) in the mammalian brain has been described.

The predominant subtype with high affinity for nicotine is comprised of  $\alpha 4$  and  $\beta 2$  subunits.

The affinity of compounds of the invention for nicotinic acetyl choline receptors have been investigated in three test for *in vitro* inhibition of  $^3\text{H}$ -epibatidin binding,  $^3\text{H}$ - $\alpha$ -bungarotoxin binding and  $^3\text{H}$ -cytisine binding as described below.

25 *In vitro* inhibition of  $^3\text{H}$ -cytisine binding (Assay I)

The predominant subtype with high affinity for nicotine is comprised of  $\alpha 4$  and  $\beta 2$  subunits. nAChRs of the latter type can selectively be labelled by the nicotine agonist  $^3\text{H}$ -cytisine.

30 Tissue Preparation

Preparations are performed at 0-4°C unless otherwise indicated. Cerebral cortices from male Wistar rats (150-250 g) are homogenised for 20 seconds in 15 ml Tris, HCl (50 mM, pH 7.4) containing 120 mM NaCl, 5 mM KCl, 1 mM  $\text{MgCl}_2$  and 2.5 mM  $\text{CaCl}_2$  using an Ultra-Turrax homogeniser. The homogenate is centrifuged at 27,000 x g for 10 minutes. The supernatant is discarded and the pellet is resuspended in fresh buffer and centrifuged a second time. The final pellet is resuspended in fresh buffer (35 ml per g of original tissue) and used for binding assays.

Assay

Aliquots of 500  $\mu\text{l}$  homogenate are added to 25  $\mu\text{l}$  of test solution and 25  $\mu\text{l}$  of  $^3\text{H}$ -cytisine (1 nM, final concentration), mixed and incubated for 90 minutes at 2°C. Non-specific binding is determined using (-)-nicotine (100  $\mu\text{M}$ , final concentration). After incubation the samples are added 5 ml of ice-cold buffer and poured directly onto Whatman GF/C glass fibre filters under suction and immediately washed with 2 x 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by con-

ventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

#### In vitro inhibition of <sup>3</sup>H-epibatidine binding (Assay II)

Epibatidine is an alkaloid that was first isolated from the skin of the Ecuadoran frog *Epipedobates tricolor* and was found to have very high affinity for neuronal nicotinic receptors, where it acts as a potent agonist. <sup>3</sup>H-epibatidine binds to two sites in rat brain, both of which have pharmacological profiles consistent with neuronal nicotinic receptors and a similar brain regional distribution [Houglings *et al.*; *Mol. Pharmacol.* 1995 48 280-287].

The high affinity binding site for <sup>3</sup>H-epibatidine is most certainly binding to the  $\alpha_4\beta_2$  subtype of nicotinic receptors. The identity of the low affinity site is still unknown; does it represent a second nicotinic receptor or a second site in the same receptor. The inability of  $\alpha$ -bungarotoxine to compete for <sup>3</sup>H-epibatidine binding sites indicates that neither site measured represents the nicotinic receptor composed of  $\alpha_7$  subunits.

#### Tissue preparation

Preparations are performed at 0-4°C unless otherwise indicated. The forebrain (+ cerebellum) from a male Wistar rat (150-250 g) is homogenised for 10-20 seconds in 20 ml Tris, HCl (50 mM, pH 7.4) using an Ultra-Turrax homogeniser. The tissue suspension is centrifuged at 27,000 x g for 10 minutes. The supernatant is discarded and the pellet is washed three times by centrifugation at 27,000 x g for 10 minutes in 20 ml fresh buffer, and the final pellet is resuspended in fresh buffer (400 ml per g of original tissue) and used for binding assays.

#### Assay

Aliquots of 2.0 ml homogenate are added to 0.100 ml of test solution and 0.100 ml of <sup>3</sup>H-epibatidine (0.3 nM, final concentration), mixed and incubated for 60 minutes at room temperature. Non-specific binding is determined using (-)-nicotine (30  $\mu$ M, final concentration). After incubation the samples are poured directly onto Whatman GF/C glass fibre filters (pre-soaked in 0.1% PEI for at least 20 min) under suction and immediately washed with 2 x 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

#### In vitro inhibition of <sup>3</sup>H- $\alpha$ -bungarotoxine binding Rat brain (Assay III)

$\alpha$ -Bungarotoxine is a peptide isolated from the venom of the Elapidae snake *Bungarus multicinctus* [Mebs *et al.*; *Biochem. Biophys. Res. Commun.* 1971 44

(3) 711], and has high affinity for neuronal and neuromuscular nicotinic receptors, where it acts as a potent antagonist.  $^3\text{H}$ - $\alpha$ -Bungarotoxine binds to a single site in rat brain with a unique distribution pattern in rat brain [Clarke *et al.*; *J. Neurosci.* 1985 5 1307-1315].

$^3\text{H}$ - $\alpha$ -Bungarotoxine labels nAChR formed by the  $\alpha_7$  subunit isoform found in brain and the  $\alpha_1$  isoform in the neuromuscular junction [Changeaux; *Fidia Res. Found. Neurosci. Found. Lect.* 1990 4 21-168]. Functionally, the  $\alpha_7$  homo-oligomer expressed in oocytes has a calcium permeability greater than neuromuscular receptors and, in some instances greater than NMDA channels [Seguela *et al.*; *J. Neurosci.* 1993 13 596-604].

#### Tissue preparation

Preparations are performed at 0-4°C unless otherwise indicated. Cerebral cortices from male Wistar rats (150-250 g) are homogenised for 10 seconds in 15 ml 20 mM Hepes buffer containing 118 mM NaCl, 4.8 mM KCl, 1.2 mM  $\text{MgSO}_4$  and 2.5 mM  $\text{CaCl}_2$  (pH 7.5) using an Ultra-Turrax homogeniser. The tissue suspension is centrifuged at 27,000 x g for 10 minutes. The supernatant is discarded and the pellet is washed twice by centrifugation at 27,000 x g for 10 minutes in 20 ml fresh buffer, and the final pellet is resuspended in fresh buffer containing 0.01% BSA (35 ml per g of original tissue) and used for binding assays.

#### Assay

Aliquots of 500  $\mu\text{l}$  homogenate are added to 25  $\mu\text{l}$  of test solution and 25  $\mu\text{l}$  of  $^3\text{H}$ - $\alpha$ -bungarotoxine (2 nM, final concentration), mixed and incubated for 2 h at 37°C. Non-specific binding is determined using (-)-nicotine (1 mM, final concentration). After incubation the samples are added 5 ml of ice-cold Hepes buffer containing 0.05% PEI and poured directly onto Whatman GF/C glass fibre filters (pre-soaked in 0.1% PEI for at least 6 h) under suction and immediately washed with 2 x 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

The results of these experiments are presented in Table 1 below.

**Table 1**  
***In vitro* Binding Activity**

Compound	Assay I IC <sub>50</sub> (μM)	Assay II IC <sub>50</sub> (μM)	Assay III IC <sub>50</sub> (μM)
3-[6-Chloro-(3-pyridaziny)]-9-methyl-3,9-diazabicyclo[4.2.1]nonane;	1.2	2.5	10
3-[6-Chloro-(3-pyridaziny)]-3,9-diazabicyclo[4.2.1]nonane;	0.02	0.18	1.4
3-[5-(Propyl-1-en-oxy)-3-pyridyl]-3,9-diazabicyclo[4.2.1]nonane;	0.002	0.002	1.8
3-(5-Ethenyloxy-3-pyridyl)-3,9-diazabicyclo[4.2.1]nonane;	0.002	0.004	1.5
3-(5-Ethoxy-3-pyridyl)-3,9-diazabicyclo[4.2.1]nonane;	<0.03	0.011	6.2
3-[5-Ethoxy-(3-pyridyl)]-9-methyl-3,9-diazabicyclo[4.2.1]nonane;	0.005	0.021	8.1
3-[5-(Propyl-1-en-oxy)-3-pyridyl]-9-methyl-3,9-diazabicyclo[4.2.1]nonane;	0.005	0.016	10.0
3-(5-Ethenyloxy-3-pyridyl)-9-methyl-3,9-diazabicyclo[4.2.1]nonane;	0.003	0.014	5.8
9-[5-Ethoxy-(3-pyridyl)]-3,9-diazabicyclo[4.2.1]nonane;	0.003	0.018	2.7
9-[5-(Propyl-1-en-oxy)-(3-pyridyl)]-3,9-diazabicyclo[4.2.1]nonane;	0.003	0.003	2.7
9-[5-Methoxy)-(3-pyridyl)]-3,9-diazabicyclo[4.2.1]nonane;	0.150	0.014	3.0

These results show the excellent binding affinity and selectivity of the compounds of the invention for the nicotinic acetyl choline receptors, in particular the nAChR subtypes α4β2.

## Claims

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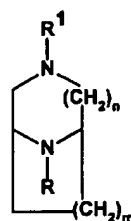
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# CLAIMS

1. A diazabicycloalkane derivative represented by the general Formula I



any of its enantiomers or any mixture thereof, an N oxide thereof, a pharmaceutically acceptable salt thereof, in a labelled or un-labelled form,

wherein,

n is 2 or 3; and

m is 1, 2 or 3; and

one of R and R<sup>1</sup> represents hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, or aralkyl; and

the other of R and R<sup>1</sup> represents a monocyclic 5 to 6 membered heterocyclic group,

which monocyclic heterocyclic group may be substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl, alkoxy, hydroxyalkoxy, alkoxyalkoxy, cycloalkoxy, cycloalkoxyalkoxy, alkenyl, alkenoxy, alkoxyalkenyl, alkynyl, alkynoxy, alkoxyalkynyl, alkylthio, alkenylthio, alkynylthio, alkylseleno, alkenylseleno, alkynylseleno, methylenedioxy, trifluoromethanesulfonyloxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, acyloxime, or a group of the formula -COOR<sup>3</sup>, -CONR<sup>2</sup>R<sup>3</sup>, -NH-CO<sub>2</sub>R<sup>2</sup>, -NHCO-R<sup>2</sup>, -OCO-NR<sup>2</sup>R<sup>3</sup>; in which formulae R<sup>2</sup> and R<sup>3</sup> independently of each another represents hydrogen or alkyl; or

which monocyclic heterocyclic group may be substituted with an aryl group, which aryl group is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or acyloxime; or

5 which monocyclic heterocyclic group may be substituted with a group of the formula  
"-X-alkyl-Y-alkyl", wherein X and Y independently of each another represents O  
(epoxy), S, NH, N-alkyl or Se, and the alkyl group is optionally substituted with alkoxy,  
10 or thioalkoxy; or

5 which monocyclic heterocyclic group may be substituted with a group of the formula  
"-X-(ALK)<sub>o</sub>-aryl", wherein X represents O, S, NH, N-alkyl or Se; "ALK" represents alkyl,  
15 alkenyl or alkynyl; o is 0 or 1; and aryl is optionally substituted one or more times with  
alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy,  
10 alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro oxime,  
alkyloxime, acyloxime; or

20 which monocyclic heterocyclic group may be substituted with a group of the formula  
"-X-(ALK)<sub>o</sub>-Z", wherein X represents O, S, NH, N-alkyl or Se; "ALK" represents alkyl,  
15 alkenyl or alkynyl; o is 0 or 1; and Z represents a 5- or 6-membered monocyclic  
heterocyclic group, which group is optionally substituted one or more times with alkyl,  
25 cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy,  
methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or  
acyloxime; or

20 which monocyclic heterocyclic group may be substituted with another monocyclic 5 to  
30 6 membered heterocyclic group, which additional heterocyclic group is optionally  
substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl,  
alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
35 25 -CN, amino, nitro, oxime, alkyloxime, or acyloxime; or

which monocyclic heterocyclic group may be substituted with a group of the formula  
40 "(ALK)<sub>o</sub>-HET", wherein "ALK" represents alkyl, alkenyl or alkynyl; o is 0 or 1; and  
"HET" represents a non-aromatic heterocyclic group; or

30 the other of R and R<sup>1</sup> represents a **bicyclic heterocyclic group**,  
composed of a 5 to 6 membered monocyclic heterocyclic group fused to a benzene  
45 ring, and

35 which bicyclic heterocyclic group may be substituted one or more times with  
alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; alkoxy-alkoxy;  
50 cycloalkoxy; alkenoxy; alkynoxy; methylenedioxy; halogen; -OH; -CF<sub>3</sub>; -OCF<sub>3</sub>; -CN;  
amino; nitro; oxime; alkyloxime; or acyloxime;



an aryl group, which aryl group is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or acyloxime;

a monocyclic 5- to 6-membered heterocyclic group, which heterocyclic group is optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CN, amino, nitro, oxime, alkyloxime, or acyloxime; or

R and/or R<sup>1</sup>, together with the nitrogen atom to which they are attached, represent an alkyl-onium salt, a dialkyl-onium salt, a cycloalkyl-onium salt, an alkyl-cycloalkyl-onium salt, a dicycloalkyl-onium salt, an alkyl-cycloalkylalkyl-onium salt, a cycloalkyl-cycloalkylalkyl-onium salt, or a dicycloalkylalkyl-onium salt.

2. The diazabicycloalkane derivative of claim 1, wherein the group bridging R and R<sup>1</sup> is a 3,9-diazabicyclo-[4.2.1]-nonane.

3. The diazabicycloalkane derivative of claim 1, wherein one of R and R<sup>1</sup> represents hydrogen or alkyl, and the other of R and R<sup>1</sup> represents a monocyclic 5- to 6-membered heterocyclic group, which heterocyclic group may be substituted with halogen, alkoxy, or alkenoxy.

4. The diazabicycloalkane derivative of claim 1, wherein R or R<sup>1</sup> represents 6-chloro-3-pyridazinyl, 5-(propyl-1-en-oxy)-3-pyridyl, 5-ethenyloxy-3-pyridyl, 5-ethoxy-3-pyridyl, or 5-methoxy-3-pyridyl.

5. The diazabicycloalkane derivative of claim 1, which is

3-[6-Chloro-(3-pyridazinyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;

3-[6-Chloro-(3-pyridazinyl)]-3,9-diazabicyclo-[4.2.1]-nonane;

3-[5-(Propyl-1-en-oxy)-3-pyridyl]-3,9-diazabicyclo-[4.2.1]-nonane;

3-(5-Ethenyloxy-3-pyridyl)-3,9-diazabicyclo-[4.2.1]-nonane;

3-(5-Ethoxy-3-pyridyl)-3,9-diazabicyclo-[4.2.1]-nonane;

3-[5-Ethoxy-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;

3-[5-(Propyl-1-en-oxy)-3-pyridyl]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;

3-(5-Ethenyloxy-3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;

9-[5-Ethoxy-(3-pyridyl)]-3,9-diazabicyclo-[4.2.1]-nonane;

9-[5-(Propyl-1-en-oxy)-(3-pyridyl)]-3,9-diazabicyclo-[4.2.1]-nonane;

9-[5-Methoxy-(3-pyridyl)]-3,9-diazabicyclo-[4.2.1]-nonane;

3-[6-Chloro-(3-pyridazinyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;

5 3-[5-Bromo-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-[5-Chloro-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-[5-Bromo-(3-pyridyl)]-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-[5-Chloro-(3-pyridyl)]-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
10 5 3-[6-Bromo-5-ethoxy-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-[6-Chloro-5-ethoxy-(3-pyridyl)]-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(3-Pyridyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-(3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
15 3-(6-Bromo-3-pyridazinyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
10 3-(6-Iodo-3-pyridazinyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(6-Bromo-3-pyridazinyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-(6-Iodo-3-pyridazinyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
20 3-(6-Chloro-3-Pyridyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-(6-Chloro-3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
15 3-(6-Bromo-3-Pyridyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-(6-Bromo-3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
25 3-(6-Fluoro-3-Pyridyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane;  
3-(6-Fluoro-3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
3-(6-Iodo-3-Pyridyl)-10-methyl-3,10-diazabicyclo-[4.3.1]-decane; or  
20 3-(6-Iodo-3-pyridyl)-9-methyl-3,9-diazabicyclo-[4.2.1]-nonane;  
30 any of its enantiomers or any mixture thereof, an N oxide thereof, a  
pharmaceutically acceptable salt thereof, in a labelled or un-labelled form.

35 6. A pharmaceutical composition comprising a therapeutically-effective amount of a  
25 diazabicycloalkane derivative of any of the claims 1-5, or a pharmaceutically-  
acceptable addition salt thereof, together with at least one pharmaceutically-  
acceptable carrier or diluent.

40 7. Use of a diazabicycloalkane derivative of any of claims 1-5, or a pharmaceutically-  
30 acceptable addition salt thereof, for the manufacture of a pharmaceutical composition  
for the diagnosis, treatment, prevention or alleviation of a disease or a disorder or a  
condition of a mammal, including a human, which disease, disorder or condition is  
responsive to the activity of nAChR modulators.  
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35 8. The use according to claim 7, wherein the disease to be treated is pain, a disease  
in the central or peripheral system, a disease caused by smooth muscle contraction,  
neurodegeneration, inflammation, chemical substance abuse or withdrawal symptoms  
50 caused by the cessation of intake of the chemical substance, such as assistance in  
the cessation of smoking.

5  
10 9. The use according to claim 7, wherein a disease in the central or peripheral system is Alzheimer's disease, Parkinson's disease, memory dysfunction or attention deficit hyperactivity disorder.

10 5  
15 10. A method of diagnosis, treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to the activity of nAChR modulators, comprising the step of administering to such a living animal body, including a human, in need thereof  
10 a therapeutically effective amount of a diazabicycloalkane derivative of any of the claims 1-5.

20 11. The method according to claim 10, wherein pain, a disease in the central or peripheral system, a disease caused by smooth muscle contraction,  
15 neurodegeneration, inflammation, chemical substance abuse or withdrawal symptoms caused by the cessation of intake of chemical substances, such as smoking  
25 cessation, is treated.

20 12. The method according to claim 10, wherein a disease in the central or peripheral system, said disease being Alzheimer's disease, Parkinson's disease, memory  
30 dysfunction or attention deficit hyperactivity disorder, is treated.

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00211

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC7: C07D 487/08, C07D 471/08, A61K 31/551, A61K 31/439, A61K 31/395, A61K 49/00, A61P 25/28, A61P 25/30, A61P 29/00 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC7: C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9740049 A1 (SANOCHEMIA LTD.), 30 October 1997 (30.10.97), page 8, line 1 - page 9, line 25 --	1-12
X	EP 0215650 A2 (PFIZER INC.), 25 March 1987 (25.03.87), page 33, line 7 - line 30; page 37, line 27 - page 39, line 24; page 40, line 12 - page 41, line 33, the claims --	1-6
X	Journal of Medicinal Chemistry, Volume 35, No 4, February 1992, Paul R. McGuirk et al, "Synthesis and Structure-Activity Relationships of 7-Diazabicycloalkylquinolones, Including Danofloxacin, a New Quinolone Antibacterial Agent for Veterinary Medicine" page 611 - page 620 --	1-6
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
21 August 2000		11.09.2000
Name and mailing address of the International Searching Authority European Patent Office P.O. Box 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel: (+31-70)340-2040, Tx 31 651 epo nl, Fax: (+31-70)340-3016		Authorized officer  GERD STRANDELL/EØ Telephone No.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00211

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9854182 A1 (NEUROSEARCH A/S), 3 December 1998 (03.12.98)  --	1-12
X	WO 9854181 A1 (NEUROSEARCH A/S), 3 December 1998 (03.12.98)  --	1-12
P,A	WO 9921834 A1 (NEUROSEARCH A/S), 6 May 1999 (06.05.99)  --	1-12
A	FR 1549235 A (CIBA SOCIETE ANONYME), 4 November 1968 (04.11.68), page 12 - page 13, example 17; page 2, right column; claims 44, 72  --	1-12
A	Eur. J. Med. Chem., Volume 22, 1987, Balkishen Razdan et al, "Studies on azabicyclo systems: syntheses and spasmolytic activity of analogues of 9-methyl-3, 9-diazabicyclo(4.2.1)nonane and 10-methyl-3, 10-diazabicyclo(4.3.1)decane" page 573 - page 577  -- -----	1-12

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 00/00211

## **Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10-12  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see next sheet**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

## **Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 00/00211

Claims 10-12 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

**INTERNATIONAL SEARCH REPORT**  
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International application No.  
**PCT/DK 00/00211**

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